23. (Once Amended) The system of claim 1 which further comprises (d) a detector circuit.

27. (Twice Amended) The method of claim 26 in which the determining step provides information on pathways or functional categories affected in the cell.

50. (Once Amended) The system of claim 1 which further comprises a second modified surface that separates the one or more electrically active cells and which comprises a layer that is repulsive to cell adherence.

REMARKS

Claims 28-49 are canceled herewith, without prejudice to pursuing the cancelled claims in this or other continuing applications. Upon entry of these amendments, Claims 1-27 and 50 will be pending and under active consideration. Claims 15, 17, 20, 22, 23, 27 and 50 have been amended. Support for the amendments to Claims 15, 17 and 20 is found in original Claim 1. Claims 22, 23, 27 and 50 have been amended to provide more clarity. Support for the amendments to Claims 22 and 50 is found in the discussion on page 16, lines 25-29, and on page 18, lines 15-18. Applicant respectfully submits that no new matter has been added. A marked-up version of the claims indicating the changes to the claims is attached hereto as Exhibit A. A newly executed supplemental Declaration is submitted herewith. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Final Office Action are respectfully requested.

The Invention

As claimed, the invention is a system comprising a solid state microelectrode, a cell culture comprising one or more electrically active cells, an intervening layer, and software that comprises instructions, which can be executed by a computer. In particular, the intervening layer is recited in Claim 1 as (i) comprising a surface modifying agent, and (ii) *positioned between the microelectrode and the one or more cells* of the cell culture such that *a high impedance seal is provided* at least in the vicinity of the one or more cells of the cell culture. Drawing the Examiner's attention to page 8, lines 11-15 of the application, as filed, the applicant has described a "high impedance" seal as one "that reduces the lateral flow of ions across the microelectrode from the surrounding medium, while permitting or facilitating the vertical flow of ions between the cell and the microelectrode. In this manner, the microelectrode is best suited to detect changes in the ion flux attributable to the cell and not due to the surrounding medium." Also, at page 9, lines 31-33 of the application, as filed, the applicant states that "such a device may further comprise an intervening layer that is acting as a high impedance seal and which is positioned between the microelectrode and the one or more cells of the cell culture, . . ." It goes without saying that any prior reference alleged to anticipate the claimed invention or any combination of references alleged to render the claimed invention obvious must recite all the elements of the claimed invention, including an intervening layer.

The Rejection of Claims 1-8, 12-14, and 23 Under 35 U.S.C. § 102(b)

Claims 1-8, 12-14, and 23 stand finally rejected as allegedly being anticipated by Jung *et al.* The Examiner apparently believes that the apparatus described in Figure 6 (a, b) of Jung *et al.* is no different from certain aspects of the claimed invention. In particular, the Examiner states at page 4 of the Final Office Action that "the Jung *et al.* reference indicates that in some cases the platinization of the microelectrode was incomplete and thus the SAM could have attached to any hydroxyl groups on the exposed surface thus meeting the 'at least in the vicinity of said one or more cells' limitation." The Examiner also writes that "the claim as written does not require that the intervening layer be attached to or in contact with the microelectrode surface." The Examiner's rejection based on Jung *et al.* is respectfully traversed for the following reasons.

Applicant agrees that the Jung *et al.* reference discloses the use of a silane SAM. Applicant further agrees that the Jung *et al.* reference discloses a microelectrode that had been platinized using platinum black. These two points are all that Applicant agrees with, however. Jung *et al.* use a silane SAM not to establish an intervening layer within the meaning of the instant claims but to establish a surface that is more accommodating of living cells. No where in the Jung *et al.* reference is the notion of establishing an intervening layer, which serves as a high impedance seal, disclosed, taught, or suggested. In fact, Applicant respectfully asserts that Jung *et al.* teaches away from the claimed intervening layer, as evidenced by their statements in the body of the reference:

> These arguments show that small electrode impedances (Z_A and Z_B) and a large amplifier internal resistance (R_{IN}) provide the best coupling of the signal. In addition, *$R<<r$ implies that the cell should be placed directly on top of the electrode with little intervening material.* That is, there should be a small

> resistance, R, between cell and electrode, and a large resistance, r, between the cell-electrode junction and the bath. Regarding the micro-electrodes themselves, the platinum deposits, which have a very rough and porous morphology, both increase the capacitance C_{ma} (lowering the reactance $[X=-jl(\omega C_{ma})]$ and *decrease the real part of the impedance* R_{ma}). *See*, page 1184, col. 2, lines 1-12 (emphasis added).

Hence, Jung *et al.* suggest that (i) there should be a small resistance between the cell and the electrode, and (ii) there should be a large resistance between the cell-electrode junction and the bath. Jung *et al.* infer that both of these objectives are allegedly accomplished by placing the cell "directly on top of the electrode *with little intervening material*." (emphasis added) Jung *et al.* further elaborate that the platinum (black) deposits lower the reactance and decrease the real part of the impedance *between the cell and the electrode.*

Jung *et al.*'s interest, therefore, lies in decreasing the impedance between the cell and the electrode. This interest is served by depositing platinum black on the surface of the electrode while establishing little intervening material between the cell and the electrode.

Contrary to what the Examiner contends, not even a fortuitous amount of silane SAM would be established on the surface of platinum black because of the absence of surface hydroxyl groups – to which the silane SAM can covalently attach. And to address the Examiner's further contention, even if the coverage of the platinum deposits is incomplete, the underlying electrode described in Jung *et al.* is elemental gold – which, likewise, would fail to provide on its surface the functional groups necessary to react with the silane SAM.

In conclusion, no intervening layer within the meaning of the pending claims is possible in the teachings of the Jung *et al.* reference, which itself suggests that little intervening material be established between the cell and the electrode.

Applicant would also like to point out that Figures 6 (a, b) of the Jung *et al.* reference and

1 (a, b) of the pending application merely illustrate an action potential recorded from a microelectrode. The illustrations in and of themselves provide no guidance or information on the claimed intervening layer, which is described in detail elsewhere in the specification of the pending application – but which is certainly not described anywhere by Jung *et al.*

Accordingly, it is believed that the rejection based on Jung *et al.* has been overcome. Applicant respectfully requests that this rejection be withdrawn.

The Rejection of Claims 1-14, 18-19, and 23-27 Under 35 U.S.C. § 103

Claims 1-14, 18-19, and 23-27 stand rejected as allegedly being rendered obvious over the proposed combination of Borkholder *et al.* and Jung *et al.* However, neither Jung *et al.* nor Borkholder *et al.* teach, suggest, or disclose an intervening layer as recited in independent Claims 1 and 24. Accordingly, the Examiner has failed to carry her burden of making a *prima facie* showing of obviousness. This rejection cannot, therefore, be reasonably sustained and should be withdrawn. The rejection having been overcome, Applicant respectfully requests favorable reconsideration of the rejected claims.

The Rejection of Claims 22, 23, 27 and 50 Under 35 U.S.C. § 112, Second Paragraph

Claims 22, 23, 27 and 50 stand rejected as being allegedly indefinite for failure to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of the claims has been amended to provide more clarity. The rejection having been overcome, Applicant respectfully requests favorable reconsideration of the rejected claims.

Applicant is Entitled to the Benefit of the Filing Date of the Provisional Patent Application

The Examiner contends that "the generic concept as disclosed in the instant specification and as recited in the claims is not disclosed in the provisional application." Applicant respectfully disagrees. The provisional application contemplates the totality of the claimed system. *See*, Section on "Specific Aims," page 39 of the priority application, a highlighted copy of which is attached hereto as Exhibit A.

As the Examiner will note, Specific Aim 1 describes the examination of the effect of test compounds on the action potential of cells and the use of algorithms (i.e., software) to decipher the differences in the action potentials. Specific Aim 2 discusses the use of surface chemistry to establish a patch-clamp like seal (i.e., a high impedance seal) between the cell and the microelectrode. Next, Specific Aim 3 "will combine the results of specific aims 1 and 2 to produce an integrated system and to validate our methodology." Interestingly, Jung *et al.* is cited as a reference for the development of an electronic platform, which was successfully tested by "recording electrical activity fro[m] single unpatterned hippocampal neurons." However, it is the provisional application that discusses the establishment of a solid state/biological "interface" that localizes the cell over a microelectrode and which possesses the requisite patch-clamp like seal. This discussion lends further evidence that Applicant contemplated the totality of the claimed invention at least as of the filing of the provisional patent application and to the fact that Jung *et al.* do not teach the claimed intervening layer.

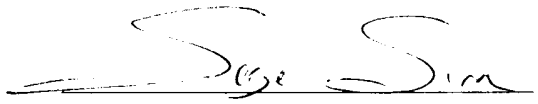
CONCLUSION

Applicant believes that the pending claims recite subject matter that is novel and non-obvious over the disclosure of the prior art of record and which satisfies all the statutory requirements of patentability. Favorable consideration of such subject matter is respectfully requested.

No fees apart from the fee for the Petition for Extension of Time are believed to be necessary. However, the Commissioner is authorized to charge any shortage in fees due in connection with the filing of this Amendment, or credit any overpayment, to Deposit Account No. 50-1710.

Respectfully submitted,

KATTEN MUCHIN ZAVIS ROSENMAN



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Date: April 2, 2003

EXHIBIT A

MARKED VERSION OF THE CLAIMS
U.S. PATENT APPLICATION NO. 09/575,377

MARKED-UP VERSION OF CLAIMS SHOWING CHANGES MADE

15. (Once Amended) [The system of claim 1 in which the]A system capable of identifying one or more ion channels of a cell, which elements are affected by a test substance, comprising a device and accompanying software,

in which said device comprises:

(a) a solid state microelectrode;

(b) a cell culture comprising one or more electrically active cells having a cell membrane including one or more ion channels, which one or more cells are capable of providing a measurable action potential that exhibits one or more perceptible characteristics; and

(c) an intervening layer which (i) comprises a surface modifying agent, and (ii) is positioned between said microelectrode and the one or more cells of said cell culture, such that a high impedance seal is provided at least in the vicinity of said one or more cells of said cell culture, said intervening layer further comprising[es] cell anchorage molecules;

and in which said accompanying software comprises instructions that can be implemented by a computer and which are capable of relating changes in the one or more characteristics exhibited by said action potential to one or more ion channels of said one or more cells upon exposure of said one or more cells to a test substance.

17. (Once Amended) [The system of claim 1 in which the]A system capable of identifying one or more ion channels of a cell, which elements are affected by a test substance, comprising a device and accompanying software,

in which said device comprises:

(a) a solid state microelectrode;

(b) a cell culture comprising one or more electrically active cells having a cell membrane including one or more ion channels, which one or more cells are capable of providing a measurable action potential that exhibits one or more perceptible characteristics; and

(c) an intervening layer which (i) comprises a surface modifying agent, and (ii) is positioned between said microelectrode and the one or more cells of said cell culture, such that a high impedance seal is provided at least in the vicinity of said one or more cells of said cell culture, said intervening layer further comprising[es] a high viscosity mixture comprising alcohols, ethers, esters, ketones, amides, glycols, amino acids, saccharides, carboxymethylsaccharides, carboxyethylsaccharides, aminosaccharides, acylaminosaccharides, polymers thereof, or combinations thereof;

and in which said accompanying software comprises instructions that can be implemented by a computer and which are capable of relating changes in the one or more characteristics exhibited by said action potential to one or more ion channels of said one or more cells upon exposure of said one or more cells to a test substance.

20. (Once Amended) [The system of claim 1 in which the cell culture is]A system capable of identifying one or more ion channels of a cell, which elements are affected by a test substance, comprising a device and accompanying software,

in which said device comprises:

(a) a solid state microelectrode;

(b) a cell culture coated with a polymer comprising one or more electrically active cells having a cell membrane including one or more ion channels, which one or more cells are capable of providing a measurable action potential that exhibits one or more perceptible characteristics; and

(c) an intervening layer which (i) comprises a surface modifying agent, and (ii) is positioned between said microelectrode and the one or more cells of said cell culture, such that a high impedance seal is provided at least in the vicinity of said one or more cells of said cell culture;

and in which said accompanying software comprises instructions that can be implemented by a computer and which are capable of relating changes in the one or more characteristics exhibited by said action potential to one or more ion channels of said one or more cells upon exposure of said one or more cells to a test substance.

22. (Twice Amended) The system of claim 1 in which the intervening layer comprises [an attractive] a layer that is attractive to cell adherence.

23. (Once Amended) The system of claim 1 which further comprises (d) a detector circuit.

27. (Twice Amended) The method of claim 26 in which the determining step [deconvolution of the action potential or its derivatives, the one or more characteristics thereof, or the one or more changes therein] provides information on pathways or functional categories affected in the cell.

50. (Once Amended) The system of claim 1 which further comprises a second modified surface that separates the one or more electrically active cells and which comprises a [repulsive] layer that is repulsive to cell adherence.

Docket No.: 215177.00101
Customer No. 27160

PATENT APPLICATION NO.
09/575,377

SUPPLEMENTAL DECLARATION

As a below named inventor, I hereby declare that:

My residence, post office and citizenship is as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) of the subject matter claimed and for which a patent is sought on the invention entitled **HIGH THROUGHPUT FUNCTIONAL GENOMICS**, the specification of which was filed with the U.S. Patent and Trademark Office on May 22, 2000, as U.S. Patent Application No. 09/575,377;

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known to me to be material to patentability in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):		**Priority Claimed**		
Number	**Country**	**Day/Month/Year filed**	**Yes**	**No**
NONE				

I hereby claim the benefit under 35 USC §119(e) of any United States provisional application(s) listed below.

Prior Provisional Application(s):

Application Number	**Filing Date**
60/135,275	May 21, 1999

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or Section 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

A. Specific Aims

There is a notable absence of accessible methodology that enables toxicology, dr screening and gene function analysis at the cellular function level *in vitro*. Also lacking many *in vitro* systems capable of chronic electrophysiological monitoring of neuronal functi We propose to develop a novel technology based on neuronal electrophysiology to create a n high-throughput method of determining a compound's effect on a cell's function where t reporter element is an array of electrically active cells. The proposal combines two basic resea ideas that are important in and of themselves but, when combined, create the potential fo powerful new tool based on a cell's function.

Specific Aim 1 will use neuronal cells - embryonic and CNS stem cell lines - as diagnostics real-time assay of a compound's function. We have demonstrated the feasibility of this conc by using living neuronal cells as sensor elements for generic toxin detection. Our work show that the majority of toxins tested stopped the action potential. However, the manner in whi the action potential was interrupted showed differences that we believe allows the determinati of which pathways were affected by a particular toxin or biochemical. The observed differences the action potential's peak shape and other characteristics are most likely due to the way t individual toxin affects different biochemical pathways that differentially effects the i channels. Algorithms to decipher these differences will be used to identify cellular functio categories, allowing aspects of its function in that cell to be deduced. We will also investig using stem cells as a final cellular assay so as to have a stable long-lived phenotype to form t basis of the final assay system.

Specific Aim 2 involves localizing the neuronal cells on the microelectrodes of a microelectro array with surface chemistry to establish a patch-clamp like seal between the cell and t microelectrode. We will tailor the solid state/biological interface using antibodies specific hippocampal neurons, and later stem cells, to make reproducible arrays of living cel Preliminary work has been reported on measuring signals from neurons using solid state devi (Regher *et al.*, 1989; Eggers *et al.*, 1990; Fromherz *et al.*, 1991; Offenhausser *et al.* 1997; Jung *et* 1998). By monitoring the electrical signals of the neurons on the microelectrodes in a defin growth system, we will be able to directly observe changes in intracellular communication from biochemical we have introduced into the culture media.

Specific Aim 3 will combine the results in specific aims 1 and 2 to produce an integrated syst and to validate our methodology. We have already developed an electronic platform to microelectrode array chip and have successfully tested it by recording electrical activity fr single unpatterned hippocampal neurons (Jung *et al.*, 1998). When Specific Aim 2 accomplished the cells can be localized on individual microelectrodes on a chip and ea individual cell now becomes a unique assay element so, statistics can be performed on reproducible cell population in response to a compound we have introduced into the med The data from the resulting analysis is now easily coupled to many current bioinformat systems.

We will validate our system in Specific Aim 3 by taking the biochemicals evaluated Specific Aim 1 and monitoring the changes in electrical potential after they have been introduc in the media. We will examine the cells at different ages of development, as well as under und an expanded range of conditions that were examined in Specific Aim 1 to show that the system consistent. Work is proceeding in a number of groups and companies to develop the circuitry analyze the signals and some rudimentary systems are commercially available. We plan to ta advantage of progress by these other groups to construct our system in Specific Aim 3.

EXHIBIT E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: James J. HICKMAN

Application No.: 09/575,377 — Group Art Unit: 1631

Filed: May 22, 2000 — Examiner: M. P. Allen

For: HIGH THROUGHPUT FUNCTIONAL GENOMICS — Attorney Docket No. 215177.00101

NOTICE OF APPEAL FROM THE PRIMARY EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

BOX AF
Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the decision dated December 03, 2002, of the Primary Examiner finally rejecting Claims 1-14, 18, 19, 23-27 and 50.

The items checked below are appropriate.

1. ■ A Petition for a One-Month Extension of Time to respond to the final rejection is enclosed. The Extension fee of $55.00 extension fee under 37 C.F.R. §1.17 should be charged to our Deposit Account No. 50-1710.

2. □ A Petition for an additional ____ month extension of time to take further action, together with the $_____ extension fee under 37 C.F.R. §1.17, was filed on

3. □ Notice of Appeal: Fee $320.00

□ Fee $160.00 should be charged to our Deposit Account No. 50-1710.

■ Enclosed

04/03/2003 CNGUYEN 00000128 09575377
02 FC:2401 160.00 OP

☐ Not required (fee paid in prior appeal)

☐ Charge to Deposit Account No. 50-1710 (One additional copy of this Notice enclosed herewith) the total fee amount of $_____.

4. ■ Any prior general authorization to charge an issue fee under 37 C.F.R. §1.18 to Deposit Account No. 50-1710 is hereby revoked. The Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. 1.16 or 1.17 which may be required during the entire pendency of this application, or to credit any overpayment, to Deposit Account No. 50-1710.

5. ■ Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

Gilberto M. Villacorta, Ph.D.
Registration No. 34,038
Serge Sira
Registration No. 39,445

Patent Administrator
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Date: April 2, 2003

EXHIBIT E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	
James J. HICKMAN	:	
Application No. 09/575,377	:	Group Art Unit: 1631
Filed: May 22, 2000	:	Examiner: M. P. Allen

For: HIGH THROUGHPUT FUNCTIONAL GENOMICS

PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. § 1.136(a)(1)

BOX AF
Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant in the aforementioned matter petitions to extend the time for response to the Office Action dated December 3, 2002, Paper Number 12, for one-month from March 3, 2003, to April 3, 2003.

Applicant's undersigned attorney may be reached in our Washington, D.C., office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

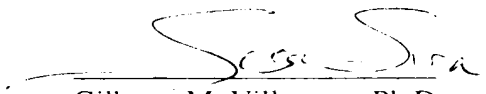
04/03/2003 CNGUYEN 00000128 09575377
01 FC:2251 55.00 OP

AUTHORIZATION

Please find enclosed a check which covers the amount of $55.00 for payment of the extension fee. Applicant believes there is no additional fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due

in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,



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Dated: April 2, 2003